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Supplemental Response to Advisory Action dated September 2, 2003

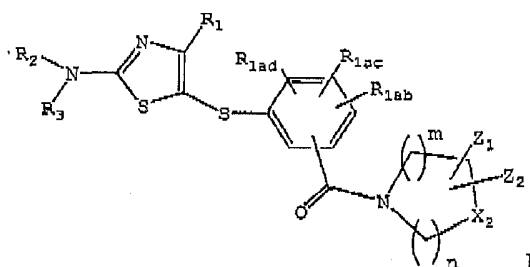
**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claims 1-6 (Canceled).

Claim 7 (Currently amended). A compound of formula I



diastereomers, enantiomers or salts thereof

where

R<sub>1</sub> is hydrogen or R<sub>6</sub>;

R<sub>1ab</sub> and R<sub>1ac</sub> are independently hydrogen, R<sub>6</sub> or -OR<sub>6</sub>;

R<sub>1ad</sub> is hydrogen;

one of R<sub>2</sub> or R<sub>3</sub> is hydrogen or alkyl and the other R<sub>2</sub> or R<sub>3</sub> is -Z<sub>4</sub>-R<sub>6a</sub>, where: Z<sub>4</sub> is -Z<sub>11</sub>-C(O)-Z<sub>12</sub>-  
and R<sub>6a</sub> is phenyl substituted with Z<sub>3</sub>;

R<sub>6</sub> is alkyl;

R<sub>1</sub>, R<sub>1ab</sub>, R<sub>1ac</sub> and R<sub>1ad</sub> are independently

- (1) — hydrogen or R<sub>6</sub>;
- (2) — OH or -OR<sub>6</sub>;
- (3) — SH or -SR<sub>6</sub>;
- (4) — C(O)<sub>q</sub>H<sub>2</sub>, C(O)<sub>q</sub>R<sub>6</sub>, or -O-C(O)<sub>q</sub>R<sub>6</sub>, where q is 1 or 2;
- (5) — SO<sub>2</sub>H or -S(O)<sub>q</sub>R<sub>6</sub>;

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- (6) —halo;  
 (7) —cyano;  
 (8) —nitro;  
 (9) — $Z_4-NR_7R_{87}$   
 (10) — $Z_4-N(R_9)-Z_5-NR_{10}R_{117}$   
 (11) — $Z_4-N(R_{12})-Z_5-R_{67}$  or  
 (12) — $P(O)(OR_6)_2$

$R_2$  and  $R_3$  are each independently H,  $Z_4-R_{6a}$ , or  $Z_4-NR_{7a}R_{8a}$ ;

$R_6$ ,  $R_{6a}$ , and  $R_{6b}$  are independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocycle, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ;

$R_{7a}$ ,  $R_{8a}$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$

- (1) are each independently hydrogen, or  $Z_4R_{6b}$ ; or  
 (2)  $R_{7a}$  and  $R_{8a}$  may together be alkylene, alkenylene, or heteroalkylene, completing a 3 to 8 membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ; or  
 (3) any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene, alkenylene or heteroalkylene completing a 3 to 8 membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

$X_2$  is  $CZ_{3a}$ ,  $NZ_{3a}$ , O or S;

$Z_{3a}$  is  $-C(O)_qZ_{6a}$ , where q is 1 H, hydroxy, optionally substituted alkyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted aralkyl,  $OZ_6$ ,  $C(O)_4H$ ,  $-C(O)_qZ_{6a}$ ,  $Z_4-NZ_7Z_8$ , or  $Z_4-N(Z_{10})-Z_5-Z_6$ ;

n is 1 to 3 2;

m is zero to 2 1;

$Z_1$  and  $Z_2$  are hydrogen;

$Z_3$  is  $-Z_4-NZ_7Z_8$ , where  $Z_4$  is alkyl;

$Z_1$ ,  $Z_2$  and  $Z_3$  are each independently

- (1) —hydrogen or  $Z_6$ ;

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(2) ~~—OH or  $\text{OZ}_{6i}$~~ (3) ~~—SH or  $\text{SZ}_{6i}$~~ (4) ~~— $\text{C}(\text{O})_q\text{H}$ ,  $\text{C}(\text{O})_q\text{Z}_{6i}$ , or  $\text{O}-\text{C}(\text{O})_q\text{Z}_{6i}$ , where  $q$  is 1 or 2,~~(5) ~~— $\text{SO}_2\text{H}$ ,  $\text{S}(\text{O})_q\text{Z}_{6i}$ , or  $\text{S}(\text{O})_q\text{N}(\text{Z}_9)\text{Z}_{6i}$~~ (6) ~~—halo,~~(7) ~~—cyano,~~(8) ~~—nitro,~~(9) ~~— $\text{Z}_4-\text{NZ}_7\text{Z}_{8i}$~~ (10) ~~— $\text{Z}_4-\text{N}(\text{Z}_9)-\text{Z}_5-\text{NZ}_7\text{Z}_{8i}$~~ (11) ~~— $\text{Z}_4-\text{N}(\text{Z}_{10})-\text{Z}_5-\text{Z}_{6i}$~~ (12) ~~— $\text{Z}_4-\text{N}(\text{Z}_{10})-\text{Z}_5-\text{H}$ ,~~(13) ~~—oxo,~~(14) ~~—any two of  $\text{Z}_4$ ,  $\text{Z}_5$ , and  $\text{Z}_6$  on a given substituent may together be alkylene or alkenylene completing a 3 to 8 membered saturated or unsaturated ring together with the atoms to which they are attached; or~~(15) ~~—any two of  $\text{Z}_4$ ,  $\text{Z}_5$ , and  $\text{Z}_6$  on a given substituent may together be  $\text{O}-(\text{CH}_2)_q-\text{O}$ ;~~ $\text{Z}_4$  and  $\text{Z}_5$  are each independently(1) ~~—a single bond,~~(2) ~~— $\text{Z}_{11}-\text{S}(\text{O})_q-\text{Z}_{12}$ ,~~(3) ~~— $\text{Z}_{11}-\text{C}(\text{O})-\text{Z}_{12}$ ,~~(4) ~~— $\text{Z}_{11}-\text{C}(\text{S})-\text{Z}_{12}$ ,~~(5) ~~— $\text{Z}_{11}-\text{O}-\text{Z}_{12}$ ,~~(6) ~~— $\text{Z}_{11}-\text{S}-\text{Z}_{12}$ ,~~(7) ~~— $\text{Z}_{11}-\text{O}-\text{C}(\text{O})-\text{Z}_{12}$ ,~~(8) ~~— $\text{Z}_{11}-\text{C}(\text{O})-\text{O}-\text{Z}_{12}$ ; or~~(9) ~~—alkyl~~ $\text{Z}_6$  and  $\text{Z}_{6a}$  is alkyl; are independently(i) ~~—alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocycle, or heterocycloalkyl;~~

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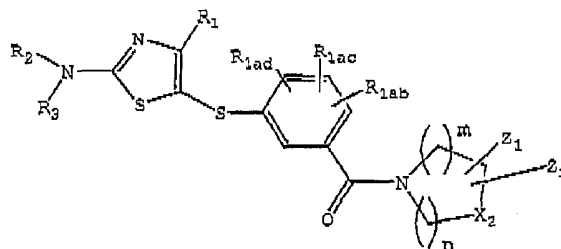
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~~(ii) a group (i) which is itself substituted by one or more of the same or different groups (i);~~

OR

~~(iii) a group (i) or (ii) which is independently substituted by one or more of the groups (2) to (15) of the definition of Z<sub>4</sub>;~~Z<sub>7</sub> and Z<sub>8</sub> are each independently hydrogen or -Z<sub>4</sub>-Z<sub>6a</sub>, where Z<sub>4</sub> is a single bond;Z<sub>7</sub>, Z<sub>8</sub>, Z<sub>9</sub> and Z<sub>10</sub>~~(1) are each independently hydrogen or -Z<sub>4</sub>-Z<sub>6a</sub>;~~~~(2) Z<sub>7</sub> and Z<sub>8</sub> may together be alkylene, alkenylene, or heteroalkylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or~~~~(3) Z<sub>7</sub> or Z<sub>8</sub>, together with Z<sub>9</sub>, may be alkylene, alkenylene, or heteroalkylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;~~Z<sub>11</sub> and Z<sub>12</sub> are each independently a single bond.~~(1) a single bond;~~~~(2) alkylene;~~~~(3) alkenylene; or~~~~(4) alkynylene;~~

Claim 8 (Previously presented). A compound of claim 7 having the formula



Claim 9 (Currently amended). A compound of claim 8 where

R<sub>2</sub> is hydrogen or alkyl; andR<sub>3</sub> is -Z<sub>4</sub>R<sub>6a</sub>, where: Z<sub>4</sub> is -C(O)- and R<sub>6a</sub> is phenyl substituted with Z<sub>3</sub>.

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~~(a)  $Z_4$  is a single bond and  $R_{6a}$  is heteroaryl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(b)  $Z_4$  is  $C(O)$  and  $R_{6a}$  is~~

~~(1) aryl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(2) alkyl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(3) cycloalkyl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ; or~~

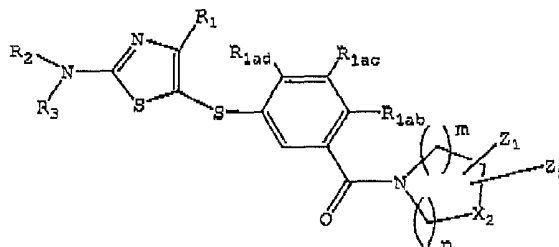
~~(4) heterocyclo optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ; or~~

~~(c)  $Z_4$  is  $C(O)O$  and  $R_{6a}$  is alkyl, cycloalkyl, aryl or aralkyl, any of which may be optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ .~~

Claim 10 (Currently amended). A compound of claim 9 wherein  $R_{1ab}$  and  $R_{1ac}$  and  $R_{1ad}$  are independently H or alkyl, ~~hydroxy, nitro, halo,  $OR_6$ ,  $NR_7R_8$ ,  $C(O)_qH$  or  $C(O)_qR_6$ .~~

Claim 11 (Original). A compound of claim 10 wherein  $R_{1ab}$  and  $R_{1ac}$  are independently alkyl.

Claim 12 (Currently amended). A compound of claim 8 having the following formula



where one of  $R_{1ab}$  and  $R_{1ac}$  and  $R_{1ad}$  is H and the other is alkyl or  $OR_6$  ~~two are independently alkyl, hydroxy, nitro, halo,  $OR_6$ ,  $NR_7R_8$ ,  $C(O)_qH$  or  $C(O)_qR_6$ .~~

Claim 13 (Currently amended). A compound of claim 12 wherein one of  $R_{1ab}$  and  $R_{1ac}$  and  $R_{1ad}$  is H and the other ~~is two are~~ independently alkyl or  $OR_6$ .

Claim 14 (Previously presented). A compound of claim 13 wherein  $R_{1ac}$  is H.

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Claim 15 (Canceled).

Claim 16 (Canceled)

Claim 17 (Previously presented). A pharmaceutical composition comprising at least one compound of claim 7 and a pharmaceutically acceptable vehicle or carrier therefor.

Claim 18 (Original). A pharmaceutical composition of claim 17 further comprising at least one additional therapeutic agent selected from anti-inflammatory agents, anti-proliferative agents, anti-cancer agents or anti-cytotoxic agents.

Claim 19 (Original). A pharmaceutical composition of claim 18 wherein the additional therapeutic agents are selected from steroids, mycophenolate mofetil, LTD<sub>4</sub> inhibitors, CTLA4-Ig, LEA-29Y, phosphodiesterase inhibitors, antihistamines, or p<sup>38</sup> MAPK inhibitors.

Claims 20 – 22 (Canceled).

Claims 23-25 (Not entered).